Drug News
藥 物 情 報

Issue Number 166

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in August 2023 with relevant information update before publish. For the latest news and information, please refer to public announcements or the website of the Drug Office of the Department of Health (http://www.drugoffice.gov.hk).

Safety Update

Australia: Medicines containing turmeric or curcumin: risk of liver injury

On 15 August 2023, the Therapeutic Goods Administration (TGA) announced that medicines and herbal supplements containing the herb Curcuma longa (turmeric) and/or curcumin may cause liver injury in rare cases. This risk also relates to other ingredients from the Curcuma species as they contain naturally occurring curcumin: Curcuma aromatica, Curcuma zanthorrhiza and Curcuma zedoaria.

The TGA had received 18 reports of liver problems experienced by consumers taking products containing Curcuma longa (turmeric) and/or curcumin up to 29 Jun 2023. Nine of these reports had enough information to suggest a liver injury that may have been caused by the Curcuma longa (turmeric) or curcumin product. Of these, in 4 cases there were no other ingredients likely to have contributed to the liver injury. Two of these cases were severe, including one that had a fatal outcome. The other 5 cases involved products that contained other ingredients that may have contributed to liver injury. In addition to these cases, there have been several Australian and overseas case reports in the scientific literature, and multiple cases reported to regulators in other countries.

In response to these reports, the TGA completed a safety investigation of the ingredients Curcuma longa (turmeric) and curcumin and the risk of liver injury. Available evidence shows that there is a rare risk of liver injury from taking Curcuma longa (turmeric) and/or curcumin in medicinal dosage forms. The risk may be higher for products with enhanced absorption or bioavailability and/or higher doses. People with existing or previous liver problems may be more likely to develop this rare adverse event. However, there is not enough information at this time to conclusively identify which medicines are higher risk. The TGA will continue to monitor this issue and is currently considering further regulatory action, including consultation on a label warning. The TGA will publish the outcome of this consultation including the details of any new labelling requirements in late 2023.

Health professionals should be aware that products containing Curcuma longa (turmeric), Curcuma aromatica, Curcuma zanthorrhiza, Curcuma zedoaria and/or curcumin may cause liver injury in some individuals. When treating patients who are presenting with symptoms of liver injury, health professionals should consider whether a complementary medicine could be involved. Use of medicines or herbal supplements containing the above Curcuma species and/or curcumin should be avoided in patients with existing or previous liver pathologies.

In Hong Kong, there is one registered pharmaceutical product containing curcuma root, namely Liver Bile Soft Gelatin Cap (Lambo) (HK-40165). The product is registered by Leeport Pharm Co Ltd. It is an over-the-counter medicine. As of the end of August 2023, the Department of Health (DH) had not received any case of adverse drug reaction related to turmeric or curcumin. As TGA is currently considering further regulatory action, the DH will remain vigilant on any safety update of the drug issued by TGA and other overseas drug regulatory authorities for consideration of any action deemed necessary.

European Union: EMA review of data on paternal exposure to valproate

On 16 August 2023, the European Medicines Agency (EMA) announced that its safety

committee, the Pharmacovigilance Risk Assessment Committee (PRAC), is reviewing data on the potential risk of neurodevelopmental disorders (NDDs) in children conceived by fathers taking valproate medicines.

The review is focusing on data from a retrospective observational study conducted by companies as an obligation following a previous review of valproate use during pregnancy.

This retrospective observational study compared the risk of NDDs (including autism spectrum disorder) in children born to men taking valproate with the risk in children born to men taking lamotrigine or levetiracetam (other treatments for epilepsy). It was carried out using multiple registry databases in Denmark, Norway and Sweden.

Initial results of the study may indicate an increased risk of NDDs in children born to men taking valproate in the three months before conception. However, the PRAC has identified important limitations with the data from the study.

In particular, the PRAC had questions about the definition of NDDs used in the study and the specific type of epilepsy the patients had. The latter is important because valproate may be prescribed more often for some types of epilepsy which are associated with NDDs.

In addition, after submitting the study results, the companies informed the PRAC about errors in the Norwegian database; the impact of these errors is not yet known. The PRAC has therefore requested companies to provide analyses of corrected data and additional information as soon as possible to address the limitations.

The PRAC will review the required data as they become available and make an EU-wide recommendation. While awaiting the outcome of the PRAC's evaluation, some Member States have implemented interim national recommendations.

Male patients being treated with valproate should not stop taking their medicine without talking to their doctor, as their epilepsy or bipolar disorder could become worse. Sudden discontinuation of treatment for epilepsy could trigger seizures. Patients who have any questions about their treatment should speak to their healthcare professional.

Previous recommendations to avoid exposure to valproate medicines in women during pregnancy due to the risk of congenital malformations (birth defects) and neurodevelopmental disorders remain in place.

In Hong Kong, there are 10 registered pharmaceutical products containing valproate. All products are prescription-only medicines. As of the end of August 2023, the Department of Health (DH) had received 15 cases of adverse drug reactions related to valproate, but these cases were not related to the risk of NDDs in children after paternal exposure to valproate.

Related news on the risks of NDDs in children after paternal exposure to valproate was previously issued by Singapore Health Sciences Authority (HSA), and was reported in Drug News Issue No. 161. The DH issued letters to inform local healthcare professionals to draw their attention on 22 March 2023. As the EMA's review is ongoing, the DH will remain vigilant on the conclusion of the review and any safety update of the drugs issued by other overseas drug regulatory authorities.

The United Kingdom: Fluoroquinolone antibiotics: Reminder of the risk of disabling and potentially long-lasting or irreversible side effects

On 30 August 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that healthcare professionals prescribing fluoroquinolone antibiotics (ciprofloxacin, delafloxacin, levofloxacin, moxifloxacin, ofloxacin) are reminded to be alert to the risk of disabling and potentially long-lasting or irreversible side effects.

Systemic and inhaled fluoroquinolones are associated with a risk of serious, disabling, long-lasting and potentially irreversible adverse reactions. These may affect different, sometimes multiple, body systems, and may include musculoskeletal, nervous, psychiatric, and sensory reactions. They have been reported in patients irrespective of their age and risk factors. Tendon damage (including the Achilles tendon but other tendons can also be involved) can occur within 48 hours of commencing treatment, or the effects can be delayed for several months and become apparent after stopping treatment.

There are no pharmacological treatments established to be effective for these disabling and potentially long-lasting or irreversible side effects. However, it is important that these symptoms are appropriately investigated, and that fluoroquinolones are stopped immediately at the first signs or symptoms of a serious adverse reaction to avoid further exposure, which could potentially worsen adverse reactions.

Restrictions to the use of fluoroquinolones were introduced in 2019 to minimise the risk of these reactions. Fluoroquinolones should not be prescribed for treatment of mild to moderate infections (such as in acute exacerbation of chronic bronchitis and chronic obstructive pulmonary disease) unless other antibiotics that are commonly recommended for these infections are considered inappropriate. Relevant situations in which other antibiotics may be inappropriate are where: there is resistance to other first-line antibiotics recommended for the infection; other first-line antibiotics are contraindicated in an individual; other first-line antibiotics have caused side effects requiring treatment to be stopped; and treatment with other first-line antibiotics has failed.

After conducting a further review, the MHRA sought the advice of the Commission on Human Medicines (CHM) on the success of existing measures to minimise the risk of disabling and potentially long-lasting or irreversible side effects of fluoroquinolones. The MHRA review involved engagement with patients and patient representatives to seek their views. It also included a review of data from a new study of fluoroquinolone prescribing in 6 European countries, including the United Kingdom, following the introduction of new restrictions for use, alongside data from other sources.

While the new study referenced above reported an overall decrease in the prescribing of fluoroquinolones in primary care in the United Kingdom, there was no evidence of a change in prescribing patterns as a result of the restrictions introduced in 2019. The study noted continued prescribing of fluoroquinolones in patients with risk factors for adverse reactions, such as patients who were concomitantly prescribed corticosteroids. The MHRA also continues to receive Yellow Card reports of these side effects, including reports where a fluoroquinolone was prescribed in situations where the product information includes a warning, or where a fluoroquinolone was prescribed for a mild or moderate infection and where an alternative antibiotic may have been appropriate. The CHM advised that it would be important to increase awareness of these risks among healthcare professionals. The MHRA will communicate in due course any additional regulatory actions in the United Kingdom as a result of this review.

Advice for healthcare professionals:

- Systemic (by mouth, injection, or inhalation) fluoroquinolones can cause long-lasting (up to months or years), disabling, and potentially irreversible side effects, sometimes affecting multiple systems, organ classes, and senses.
- Despite new restrictions and precautions introduced in 2019, a new study has shown no evidence of a change in fluoroquinolone prescribing patterns in the United Kingdom, and the MHRA has continued to receive Yellow Card reports of these side effects.
- Advise patients to stop treatment at the first signs of a serious adverse reaction, such as tendinitis or tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy, and central nervous system effects, and to contact their doctor immediately for further advice.
- Do not prescribe fluoroquinolones: for non-severe or self-limiting infections, or non-bacterial conditions, for example non-bacterial (chronic) prostatitis; for mild to moderate infections (such as in acute exacerbation of chronic bronchitis and chronic obstructive pulmonary disease) unless other antibiotics that are commonly recommended for these infections are consider inappropriate.
- Do not prescribe ciprofloxacin or levofloxacin for uncomplicated cystitis unless other antibiotics that are commonly recommended are considered inappropriate.
- Avoid fluoroquinolone use in patients who have previously had serious adverse reactions with a quinolone antibiotic (for example, nalidixic acid) or a fluoroquinolone antibiotic.
- Prescribe fluoroquinolones with special caution for people older than 60 years and for those with renal impairment or solid-organ transplants, because they are at a higher risk of tendon injury.
- Avoid use of a corticosteroid with a fluoroquinolone since coadministration could exacerbate fluoroquinolone-induced tendinitis and tendon rupture.

In Hong Kong, there are registered pharmaceutical products containing systemic fluoroquinolones for use in human, including ciprofloxacin (51 products), levofloxacin (46 products), moxifloxacin (6 products), norfloxacin (3 products), ofloxacin (15 products) and prulifloxacin (one product). All products are prescription-only medicines.

As of the end of August 2023, the Department of Health (DH) had received adverse drug reaction related to levofloxacin (13 cases; of which 3 cases were related to tendinitis and/or neuropathy) and ofloxacin (4 cases; all cases were related to suicide/suicide attempt). The DH had received adverse drug reaction related to ciprofloxacin (one case) and moxifloxacin (one case), but these cases were not related to the disabling side effects mentioned in the above MHRA's announcement. The DH had not received any case of adverse drug reaction related to norfloxacin and prulifloxacin.

Related news on the risk of musculoskeletal, nervous and psychiatric adverse reactions associated with the use of fluoroquinolones was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 25, with the latest update reported in Drug News Issue No. 163. The DH issued letters to inform local healthcare professionals to draw their attention on 8 November 2011, 16 August 2013, 13 May 2016, 11 July 2018 and 8 October 2018.

In June 2019, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided that the sales pack labels and/or package inserts of locally registered pharmaceutical products containing fluoroquinolones for systemic use should contain safety information about the risk of disabling and potentially irreversible serious adverse reactions (including tendinitis and tendon rupture, peripheral neuropathy and central nervous system effects). The DH will remain vigilant on any safety update of the drugs issued by other overseas drug regulatory authorities.

The United Kingdom: Methotrexate: advise patients to take precautions in the sun to avoid photosensitivity reactions

On 30 August 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that photosensitivity reactions are known side effects of methotrexate treatment and can be severe. Patients should be advised to take precautions to protect their skin in the sun.

The MHRA has recently received a Coroner's report following a case of a photosensitivity reaction in a patient on methotrexate. This reaction was found to have contributed to death by secondary infection. As a result of this, the MHRA has reviewed the information available to healthcare professionals and patients regarding these reactions and sought advice from the Pharmacovigilance Expert Advisory Group (PEAG) of the Commission on Human Medicines.

Photosensitivity reactions are established side effects of methotrexate treatment and are currently listed in the product information, including the Patient Information Leaflet. However, the PEAG was concerned that it is not a well-known side effect and many patients may not be aware of the additional risks of sun exposure during methotrexate treatment.

Prescribers and pharmacists are reminded to inform patients of the risk of photosensitivity reactions and to advise them to use a product with a high sun protection factor and clothing that covers the skin when in the sun. The MHRA is working with Marketing Authorisation Holders of methotrexate medicines to provide updates to the product information as appropriate.

Photosensitivity reactions often look and feel like sunburn. They can leave sun-exposed skin with a rash, redness, swelling, blisters, red bumps or oozing lesions. Severe cases can cause secondary skin infection. Photosensitivity reactions fall into two categories: phototoxic reactions and photoallergic reactions. In phototoxic reactions, a drug is activated by exposure to UV light and causes damage to the skin that can look and feel like a sunburn or a rash. These reactions can happen within minutes or after hours of exposure and are usually limited to the skin that has been exposed. Photoallergic reactions occur when UV rays interact with the ingredients in medicines or other products applied directly to the skin. The body's immune system recognizes changes caused by sun exposure as a foreign threat. The body produces antibodies and attacks, causing a reaction. These reactions are distinct from "recall" reactions where radiation-induced dermatitis and sunburn can reappear on re-exposure to radiation and sunlight while on methotrexate therapy.

Advice for healthcare professionals:

- Photosensitivity reactions (which include phototoxicity, where a drug is activated by exposure to UV light and causes damage to the skin that can look and feel like a sunburn or a rash) are known side effects of methotrexate treatment and can occur with both low-dose and high-dose treatment.
- Reactions manifest as severe sunburn such as rashes with papules or blistering, with some patients reporting swelling; rarely, photosensitivity reactions have contributed to deaths from secondary infections.
- Healthcare professionals, including those prescribing and dispensing methotrexate, should remind patients to take precautions to protect themselves from the sun and UV rays.

In Hong Kong, there are 10 registered pharmaceutical products containing methotrexate. All products are prescription-only medicines. As of the end of August 2023, the Department of Health (DH) had received 90 cases of adverse drug reaction related to methotrexate, but these cases were not related to photosensitivity reactions.

The product inserts of the above locally registered pharmaceutical products containing methotrexate include safety information about photosensitivity reactions. The risk of photosensitivity reactions associated with the use of methotrexate is also documented in overseas reputable drug references such as the "Martindale: The Complete Drug Reference". The DH will remain vigilant on any safety update of the drug issued by other overseas drug regulatory authorities.

The United Kingdom: Valproate: re-analysis of study on risks in children of men taking valproate

On 30 August 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced an update on a retrospective observational study on the risk to children born to men who took valproate in the 3 months before conception and on the need for the re-analysis of the data from this study before conclusions can be drawn.

The MHRA has kept under close review the possibility of risks to children associated with paternal exposure to valproate (in other words, whether a child could be affected if a father was taking valproate). Two studies were conducted by researchers in 2013 that did not find evidence of an increased risk to children with paternal use of epilepsy medicines, but the studies had limitations. As part of the outcome of the 2018 European review of valproate, a new retrospective study was requested from the marketing authorisation holders to examine this risk.

The study report submitted to the MHRA and to other regulatory authorities suggested an increased risk of neurodevelopmental disorders in children whose fathers took valproate during the 3-month period before they were conceived compared to children whose fathers had taken the antiseizure medicines lamotrigine or levetiracetam. However, the MHRA was subsequently informed of errors in the study that may impact on the results. A full re-analysis is required before conclusions can be drawn. As soon as the revised study analysis is available, it will be re-assessed by the MHRA.

No action is currently needed from patients. No one should stop taking valproate without advice from their specialist.

Advice for healthcare professionals:

- The MHRA continues to rigorously review all emerging data on valproate-containing medicines including findings from a retrospective observational study suggesting an increased risk of neurodevelopmental disorders in children whose fathers took valproate in the 3 months before conception, compared to those whose fathers took lamotrigine or levetiracetam.
- However, errors have been subsequently identified in the study that may impact on the results; a full re-analysis is required before conclusions can be drawn.
- As soon as the revised study analysis is available, it will be carefully re-assessed by the MHRA, and any further guidance will be communicated to patients and healthcare professionals as soon as possible.
- For female patients, continue to follow the existing strict precautions related to the known and significant harms of valproate in pregnancy.
- General practitioners and pharmacists should continue to provide repeat prescriptions for valproate; patients currently taking valproate must be advised not to stop taking it unless they are advised by a specialist to do so.

In Hong Kong, there are 10 registered pharmaceutical products containing valproate. All

Safety Update

products are prescription-only medicines. As of the end of August 2023, the Department of Health (DH) had received 15 cases of adverse drug reactions related to valproate, but these cases were not related to neurodevelopmental disorders in children after paternal exposure to valproate.

Related news on the risk of neurodevelopmental disorders in children after paternal exposure to valproate was previously issued by various overseas drug regulatory authorities, and was reported in Drug News Issue No. 161. The DH issued letters to inform local healthcare professionals to draw their attention on 22 March 2023. The DH will remain vigilant on any safety update of the drug issued by MHRA and other overseas drug regulatory authorities for consideration of any action deemed necessary.

Drug Recall

Recall of three Apo-Acyclovir products and Apo-Amitriptyline tablets due to presence of impurity

On 14 August 2023, the Department of Health (DH) endorsed a licensed drug wholesaler, Hind Wing Co Ltd (Hind Wing), to recall a total of four batches of the following four products from the market as a precautionary measure due to the presence of impurity in the products.

Name of product	Hong Kong registration number	Batch number
Apo-Acyclovir Tablets 200mg	HK-43427	TK5832
Apo-Acyclovir Tablets 400mg	HK-58229	TH6096
Apo-Acyclovir Tablets 800mg	HK-58228	TK1734
Apo-Amitriptyline Tablets 10mg	HK-09273	RM0518

The DH received notification from Hind Wing that the overseas manufacturer of the products is recalling the above batches due to the presence of a higher than accepted level of an impurity, N-nitrosodimethylamine (NDMA), in the above Apo-Acyclovir products, and an impurity, N-Nitrosonortriptyline (NNORT), in the above Apo-amitriptyline tablets. Both NDMA and NNORT are classified as a probable human carcinogen based on results from laboratory tests. As a precautionary measure, Hind Wing is voluntarily recalling the affected batches of products from the market.

The above products are all prescription medicines. The Apo-Acyclovir products containing aciclovir are used for the treatment of infections due to herpes simplex virus or varicella-zoster virus whereas the Apo-Amitriptyline tablets containing amitriptyline are used for the treatment of depression. According to Hind Wing, the above batches of products had been imported into Hong Kong. The affected Apo-Acyclovir products had been supplied to DH clinics, private doctors and pharmacies, while the affected Apo-amitriptyline tablets had been supplied to the Hospital Authority, private hospitals and re-exported to Macao.

As of the end of August 2023, the DH had not received any adverse reaction reports in connection with the products. A press release was posted in the Drug Office website on 14 August 2023 to alert the public of the product recall. The DH will closely monitor the recall.

Drug Incident

Two women arrested for suspected illegal sale and/or possession of virility product with undeclared controlled drug ingredient

On 7 August 2023, the Department of Health (DH) conducted an operation against the sale of a virility product, namely HE-MINT, which was found to contain an undeclared controlled drug ingredient. During the operation, two women aged 22 and 40 were arrested by the Police for suspected illegal possession, while one of them was also arrested for suspected illegal sale, of Part 1 poisons and unregistered pharmaceutical products.

Acting upon intelligence, the DH purchased a sample of the above product from a retail shop in Tsuen Wan for analysis. Test results from the Government Laboratory revealed that the sample contained tadalafil, which is a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138). The product is also suspected to be an unregistered pharmaceutical product. The DH's investigation is continuing.

Drug Incident

Tadalafil is used for treatment of erectile dysfunction and should only be used under the advice of a doctor. Side effects of tadalafil include low blood pressure, headaches, vomiting, dizziness and transient vision disturbances. It may interact with some drugs (such as nitroglycerin for treatment of angina) and cause a decrease in blood pressure to dangerous levels. Improper use of tadalafil may pose serious health risks, especially for patients with heart problems.

A press release was posted in the Drug Office website on 7 August 2023 to alert the public of the drug incident.

Public urged not to buy or use topical product containing undeclared controlled drug ingredients

On 15 August 2023, the Department of Health (DH) appealed to the public not to buy or use a topical product (labelled as "癬康王草本乳膏" with no English name), as it was found to contain undeclared controlled drug ingredients.

Acting upon a case referred by the Hospital Authority, the DH earlier purchased a sample of the above product from a premises in Lai Chi Kok for analysis. Test results from the Government Laboratory revealed that the product sample contained clobetasol propionate, miconazole and terbinafine, which are Part 1 poisons under the Pharmacy and Poisons Ordinance (Cap. 138). The product is also suspected to be an unregistered pharmaceutical product.

The DH conducted an operation with the Police against the above premises on 15 August 2023. During the operation, one woman aged 57 years was arrested by the Police for suspected illegal sale and possession of Part 1 poison and unregistered pharmaceutical product. The DH's investigation is continuing.

Clobetasol propionate is a steroid substance for treating inflammation. Inappropriate application of steroids could cause skin problems and systemic side effects such as moon face, high blood pressure, high blood sugar, adrenal insufficiency and osteoporosis. Products containing clobetasol propionate are prescription medicines that should be used under a doctor's directions and be supplied in a pharmacy under the supervision of a registered pharmacist upon a doctor's prescription. Miconazole and terbinafine are used for the treatment of fungal infections with side effects including local irritation and sensitivity reactions.

A press release was posted in the Drug Office website on 15 August 2023 to alert the public of the drug incident.

A product containing any western drug ingredient must be registered under the Pharmacy and Poisons Ordinance before it can be sold in Hong Kong. Part 1 poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part 1 poisons and unregistered pharmaceutical products are offences under the Pharmacy and Poisons Ordinance (Cap. 138). The maximum penalty is a fine of $100,000 and two years' imprisonment for each offence. Antibiotics can only be supplied at registered pharmacies by registered pharmacists or under their supervision and upon a doctor's prescription. They should only be used under the advice of a doctor. Illegal sale or possession of antibiotics are offences under the Antibiotics Ordinance (Cap. 137) and the maximum penalty is a $50,000 fine and one year's imprisonment for each offence.

Under the Import and Export Ordinance (Cap. 60), pharmaceutical products must be imported or exported under and in accordance with an import or export licence issued under the Import and Export Ordinance. Illegal import or export of pharmaceutical products are offences under the Import and Export Ordinance (Cap. 60) and the maximum penalty is a fine of $500,000 and 2 years' imprisonment.

All registered pharmaceutical products should carry a Hong Kong registration number on the package in the format of "HK-XXXXX". The products mentioned in the above incidents were not registered pharmaceutical products under the Ordinance in Hong Kong. Their safety, quality and efficacy cannot be guaranteed. Members of the public were exhorted not to use products of unknown or doubtful composition. They should stop using the aforementioned products immediately if they had them in their possession and to consult healthcare professionals if they felt unwell after taking the products. The products should be destroyed or disposed properly, or submitted to the Department's Drug Office during office hours.

Update on Drug Office's website: You can now search the newly registered medicines in the past year at http://www.drugoffice.gov.hk/eps/drug/newsNRM60/en/healthcare_providers?pageNoRequested=1.

Details of ALL registered pharmaceutical products can still be found in the Drug Office website at http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/

Useful Contact

Drug Complaint:

Tel: 2572 2068
Fax: 3904 1224
E-mail: pharmgeneral@dh.gov.hk

Adverse Drug Reaction (ADR) Reporting:

Tel: 2319 2920
Fax: 2319 6319
E-mail: adr@dh.gov.hk
Link: http://www.drugoffice.gov.hk/adr.html

Post: Adverse Drug Reaction and Adverse Event Following Immunization Unit,
Drug Office, Department of Health,
Room 1856, 18/F, Wu Chung House,
213 Queen's Road East,
Wanchai, Hong Kong

The purpose of Drug News is to provide healthcare professionals with a summary of local and overseas drug safety news released. Healthcare professionals are advised to keep update with the information and provide corresponding advice or therapeutic measure to patients and public.